ACRO
ASSOCIATION OF CLINICAL
RESEARCH ORGANIZATIONS

Statement Presented to

Food and Drug Administration Public Hearing

On

Reporting of Adverse Events to Institutional Review Boards

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On behalf of the Association of Clinical Research Organizations

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Introduction

Good morning. My name is Paul Covington. I am a physician and Executive Vice President for Development with PPD, a leading clinical research organization or CRO, which is headquartered in Wilmington, North Carolina. In my role at PPD I oversee medical and regulatory affairs services, including pharmacovigilance, medical writing, program management and product development. My personal research interests include diabetes, cardiology and critical care, and I have been closely involved with establishing effective monitoring processes for patient safety and data integrity in complex studies involving extremely ill patients. Prior to joining PPD in 1991, I served in various medical roles in both hospital and private practice settings, and participated as the principal investigator in several industry-sponsored clinical trials.

I appear today on behalf of ACRO, the Association of Clinical Research Organizations. As you know, clinical research organizations (CROs) assist pharmaceutical,

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biotechnology and medical device companies with the conduct of thousands of clinical trials each year, and are a key participant in the development of new drugs and new treatments. ACRO was formed in 2002 to represent this key segment of the clinical research enterprise to legislative and regulatory bodies. ACRO member companies employ more than 40,000 people worldwide, conduct research in 60 countries, and represent a multibillion-dollar industry.

The safety of human participants in clinical research is a core issue for ACRO members, and the Association applauds your solicitation of information regarding how IRBs obtain and review information about adverse events currently, and to hear ideas about how the process might be improved to better facilitate the real purposes of IRB review – to "assure the protection of the rights and welfare of the human subjects" and to make sure that "risks to subjects are minimized". On behalf of ACRO, I will briefly lay out two concrete and related suggestions to assist IRBs in their role of protecting human subjects: first, that the FDA and the stakeholders, including sponsors, institutions and others, move promptly toward standardizing the collection of safety data; and, second, that for all medium to large randomized studies, and all multi-center trials, the sponsor of the research provide standardized tabular summaries of safety data to the IRBs responsible for continuing review.

These suggestions and my comments today are informed by a recent project undertaken by the Association in response to the FDA's Critical Path initiative in which we are aiming to develop templates for standardized case report forms, including an adverse event reporting form, and, in addition, build upon feedback submitted by ACRO in October of 2003 to the agency's proposed rule regarding "Safety Reporting Requirements for Human Drug and Biological Products".

Providing adverse event information to IRBs and facilitating meaningful review

Let me begin by pointing out that today there is an extraordinary variability in the structure and content of the forms and processes utilized by investigators, sponsors, IRBs and others for the reporting and exchange of information regarding adverse events that occur during the conduct of clinical investigations. While a small part of this variability may result from unusual research designs or protocols or patient populations, the multiplicity of unique and non-standard adverse event report forms and processes is, we believe, largely unnecessary and introduces inefficiency and potential error into an already complicated data collection process. In a time when most studies involve multiple sites and multiple IRBs this idiosyncratic approach to the collection and review of essential safety data too often leads to confusion across sponsors, investigators, research sites and IRBs.

As we reviewed the varied case report forms encountered by CROs in our work with sponsors, investigators and institutions, the member companies of ACRO came to believe that an adverse event case report form could, with input from the stakeholders and guidance from the agency, be 'standardized' in reasonably short order. To demonstrate that such 'standardization', which would benefit all the stakeholders, could be achieved, ACRO has, in fact, drafted a 'standardized' adverse event case report form that we

believe could be modified as desired and adopted on a voluntary basis. In developing this proposed adverse event report form, our project team was guided by certain general principles: 1) that the format and content of an AE form should facilitate the collection of required and relevant data, and not include unnecessary or extraneous information; 2) that a standardized form should be clear, user-friendly and allow greater ease of timely reporting by investigators and sponsors and review by IRBs; and 3) that any proposed standardized AE reporting form should recognize and be consistent with regulatory requirements (of 21 CFR Parts 50, 56, 312 and 812), as well as with the recommendations and agreements of leading standards setting organizations, including the International Conference on Harmonisation (ICH), the Council for International Organizations of Medical Sciences (CIOMS) and the Clinical Data Interchange Standards Consortium (CDISC).

As I expect that ACRO will discuss our work on a proposed adverse event case report form template with the agency and with other stakeholders, including IRBs, further in the future, I will not go into further detail on that project today. (However, I will be pleased to provide additional written materials regarding a standardized AE reporting form to members of the panel, if requested.)

While ACRO has devoted the resources for the development of prototype AE and concomitant medication case report forms, to date the Association has not undertaken further work on the standardization of data collection forms, especially the additional information needed by sponsors and IRBs alike for the processing of serious adverse events (SAEs). Based on our recent contacts with standards-setting organizations like CDISC, ACRO believes that almost all the stakeholders recognize the significant advantages to be realized from increased standardization of data collection, transmission, review and analysis, and we urge the FDA to encourage and foster collaboration by the affected stakeholders, including IRBs, institutions and sponsors, to develop standardized SAE forms and processes as promptly as possible.

While the background material for today's hearing focused, rightly I believe, on concerns about excessive volumes of adverse event report being sent to IRBs, let me note, first, that in its comment to the FDA's proposed rule on "safety reporting requirements for human drug and biological products", ACRO supported the implementation of safety reporting definitions and standards consistent with those recommended by the ICH. Thus, even as we noted the potential for a significant increase in adverse event reporting and a consequent exacerbation of potential noise-to-signal problems, ACRO offered its support to a definitional change that would define "reasonable possibility" as meaning that "the relationship cannot be ruled out." Specifically, ACRO agreed that a suspected adverse drug reaction (SADR) occurs when, "A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out."

In its proposed rule on safety reporting requirements, the FDA stated that "with regard to clinical studies of investigational and marketed drugs and biological products, the proposed definition of SADR is likely to result in an increase in the number of safety reports that are currently submitted" and ACRO expressed concern about the potential

outcome that IRBs could be inundated by written safety reports of serious adverse drug reactions that were unexpected, especially in medium-to-large, multi-center, phase III trials. For this subset of clinical trials, we suggested an approach to SAE reporting and review that would allow IRBs and other stakeholders to focus on safety trends rather than isolated events, reduce IRB workload while improving IRB decision making, and assure the agency of adequate IRB safety oversight. Our proposal would require any sponsor, private or public, of medium-to-large, or multi-center, randomized studies (for example, of greater than 150 total patients) to provide to the reviewing IRB(s) regular (e.g., monthly, bimonthly, quarterly, other), partially blinded, standardized tabular summaries of all serious SADRs, sorted using standard coding dictionaries. Here, partially-blinded tabular summaries imply data assigned to group A, group B, etc., but without identifying what group A or group B are. Sponsors, IRBs, and other stakeholders could then make appropriate decisions based on differences between groups without complete unblinding. Under this approach the FDA could still define certain individual events as "always expedited reports" requiring immediate IRB notification. Meanwhile, for smaller or non-randomized studies the current safety reporting system would be retained.

This approach to safety reporting for medium-to-large trials would decrease the number of isolated IND safety reports and produce more relevant information for decision processing. It would not address the continued flow of isolated expedited safety reports from smaller, non-randomized studies nor the issue of expedited reports from other sources, such as post-marketing spontaneous reports for products already approved which are being studied for additional indications. We recognize, too, that this proposal is not without caveats, such as: 1) how will stakeholders respond to partially unblinded information? 2) how often would IRBs respond to summary information by requesting further details (especially complete unblinding) in response to minor differences across groups? 3) will IRBs choose not to act on this information, instead requesting formal Data Safety Monitoring Committees for virtually all studies and following their guidance? 4) how will the current predominantly paper-based system for SAE reporting be able to respond rapidly enough to meet the needs of a "frequent tabular summary", or does this approach dictate the shift to pure electronic capture of all SAEs?

Conclusion

Since its inception, ACRO has advocated for the development of uniform human research subject protection requirements that would apply to all research subject to Federal oversight, regardless of the source of funding for the research or the site where the research is conducted. We urge the panel to work with the NIH and other Federal agencies to ensure that safety reporting requirements for investigators, sponsors, institutions, IRBs and others be harmonized as much as possible. We believe that all participants in the research enterprise must be fully committed to the protection of research participants, and encourage you to consider our suggestions for facilitating the reporting of meaningful safety data to institutional review boards and fostering better safety review by those IRBs.

Thank you for the opportunity to appear before you today. I will be happy to answer any questions.